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Prognostic Factors in Angiosarcoma: A Multivariate Analysis of 55 Cases

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Data for prognostic factors in angiosarcoma (AS) are limited, prompting a large-scale study of AS with multivariate analysis. To analyze prognostic factors in angiosarcoma (AS), clinical and histologic findings in 55 patients collected from hospitals in Japan were reviewed. Prognostic factors were evaluated by univariate and multivariate Cox's proportional hazards models. The study involved 32 males and 23 females, ages 18–93 (median, 69) years. The primary sites of tumors included head and neck (32 cases), trunk (10), extremities (3), spleen (3), breast (3), and other (4). The overall 2-year survival rate was 21%. Univariate analysis of clinical factors including age, sex, size and depth of tumor, tumor-related symptoms, interval between onset of symptoms and admission, surgical procedures, adjuvant chemotherapy, and adjuvant radiotherapy showed that age, tumor size, and mode of treatment were significant for survival. Histologic factors analyzed were mitotic counts, cellularity, cellular pleomorphism, extent of necrosis, vascular differentiation, and nonspecific diagnosis. Only mitotic counts were significant for prognosis. Multivariate analysis on these four factors revealed that tumor size, mode of treatment, and mitotic counts were independent prognostic factors.

KEY WORDS: **angiosarcoma, prognostic factors, survival, univariate analysis, multivariate analysis**

INTRODUCTION

Malignant vascular tumors include hemangiosarcoma and lymphangiosarcoma. Because distinction between these two diseases is not only difficult but arbitrary [1,2], the all-inclusive term "angiosarcoma" (AS) is generally used. Skin and superficial soft tissues are the most common primary sites, and much less frequently, deep tissues and the viscera are involved. In general, AS has the poorest prognosis among all soft tissue sarcomas (STS) [3–7]: several studies suggested that tumor size [3–5], duration of symptoms [3], mitosis [3], presence or absence of lymphoid infiltrates [4], histologic grade [6–8], mode of treatment [9,10], and occurrence of metastasis at presentation [10] are prognostic factors. These studies, however, reported the results of univariate analysis on relatively small numbers of cases and even combined AS and hemangiopericytoma. Therefore, a large-scale study of AS with multivariate analysis was needed.

Because AS is a rare disease among STS, we collected 55 cases of AS by a nationwide study in Japan [11] and prognostic factors were estimated by multivariate analysis.

MATERIALS AND METHODS

Patients

Through reviewing the *Annual of Pathological Autopsy Cases in Japan* between 1974 and 1990, 255 patients

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originally diagnosed as having malignant vascular tumors were selected. These patients were treated at 178 institutes in Japan. We asked the pathologists in these institutes to allow us to study their cases and obtained clinical data and histologic materials of the primary lesion from 142 of these 255 patients (56%). Another 16 patients treated at the same institutes were also included. All of the histologic specimens were fixed in 10% formalin and routinely processed for paraffin-embedding. One to 20 sections per case (mean 6 sections) were examined. Histologic sections, cut at 4 μm, were stained with hematoxylin and eosin and immunohistochemical procedures (ABC method). Used antibodies Factor VIII-RA and CD-31 (Dakopatts, Copenhagen, diluted at 1:50, respectively), and UEA-1 (Vector Laboratories, Burlingame, CA, diluted at 1:4,000) are directed against vascular endothelial cells [12–14], HMB-45 (Dakopatts, diluted at 1:50) against melanocytes [15]. Diagnostic criteria for AS were as follows: (1) varying degrees of vasoformative pattern of growth, well-developed vascular channels, slitlike irregular spaces covered by large cells with hyperchromatic nuclei, or ill-defined vascular lumina with occasional vacuolization in the cytoplasm of the proliferating cells, (2) positive reactions of the proliferating cells for Factor VIII-RA, UEA-1, and/or CD-31 but negative for HMB-45. Out of 158 cases, 114 (72%) examined were diagnosed as AS. Pathologic diagnosis of the excluded cases was malignant fibrous histiocytoma (6 cases), hemangiopericytoma (6), synovial sarcoma (5), hemangioblastoma of cerebellum (5), epithelial malignancy (5), malignant lymphoma (3), leiomyosarcoma (2), hemangioma (2), nasal polyp (2), granuloma pyogenicum (1), primitive neuroectodermal tumor (1), Kaposi's sarcoma (1), leiomyoma (1), and meningioma (1). Definite diagnosis was impossible in three cases because of inadequate specimens. Fifty-six patients with metastasis at first admission or primary tumors in the liver or heart were excluded from the present study. Three patients with inadequate clinical data were also excluded. The remaining 55 patients, 42 cases from the *Annual* and 13 additional cases, were selected for further study.

Clinical Analysis

Clinical findings including sex, age, location of tumor, size and depth of tumor, tumor-related symptoms, interval between onset of symptoms and admission, surgical procedure, adjuvant chemotherapy and radiotherapy, pattern of recurrence, occurrence of metastasis, and follow-up data were available in all cases. There were 32 males and 23 females, ages 18–93 (median 69) years. Primary site of tumors are listed in Table I. The head and face (32 cases) was the most common primary site. The sites of tumor were categorized into two groups: head and face (32 cases) and other sites (23 cases). The tumor size at the initial diagnosis was 5 cm or less in 30 cases and >5 cm in 25. Forty tumors were situated superficially (i.e., superficial to the deep fascia indicating cutaneous tumor), and 15 were deeply situated. Tumor-related symptoms such as pain, inflammatory signs, or neurologic disturbance were present in 24 patients. The interval between the onset of symptoms and admission was <1 year in 43 cases and >1 year in 12. Metastasis developed during the course of the disease in 85% of patients.

TABLE I. Primary Location of Tumor in 55 Patients With Angiosarcoma

Location of tumor	No.
Head and face	32
Trunk	10
Extremities	3
Spleen	3
Breast	3
Bone	1
Retroperitoneal cavity	1
Intracranial cavity	1
Urinary bladder	1
Total	55

The mode of treatment according to the criteria of Enneking et al. [16] is shown in Table II. The number of patients treated by surgery and chemotherapy was 40 and 35, respectively. Since our study is retrospective and the cases were collected by the nationwide study, chemotherapy was given at random. Chemotherapeutic agents consisted mainly of Adriamycin (ADR) with or without *cis*platinum (CDDP) or cyclophosphamide plus vincristine (VCR) plus ADR plus DTIC (CYVADIC). Interleukin-2 was given to 21 cases. The dose of IL-2 ranged from 3.6×10^4 to 1.3×10^8 U (mean, 2.9×10^7 U). Radiotherapy was given to 32 patients, four of whom received radiotherapy alone. The radiation doses ranged from 1 to 128 Gy (mean, 41 Gy). Two patients did not receive any kind of therapy. Forty-seven patients died due to tumor: autopsy revealed dissemination of the tumors to the lung in 38 cases, bone in 21, liver in 21, regional lymph nodes in 14, adrenal gland in 14, pleura in 10, and other sites in 25.

Histologic Analysis

Without knowing the follow-up data, histologic sections were reviewed independently by two pathologists (N.N. and K.A.). Various histologic factors including cellularity, cellular pleomorphism, number of mitotic figures, degree of tumor necrosis, degree of vascular differentiation such as well-, moderately, and poorly differentiated type, and nonspecific histologic diagnosis such as spindle cell, small round cell, pleomorphic, myxoid, and unclassified tumor were evaluated as previously described in our histopathologic study of a large series of STS [17,18].

TABLE II. Mode of Treatment of 55 Patients With Angiosarcoma*

Types of surgery	Surgery alone	Surgery and adjuvant chemotherapy	Surgery and adjuvant radiotherapy	Surgery and adjuvant chemo- and radiotherapy	Total no. patients
Intralesional excision	1	2	0	2	5
Marginal excision	4	3	5	5	17
Wide local excision	4	5	0	6	15
Amputation	0	1	0	2	3
Total	9	11	5	15	40

*Excluded: 2 patients who did not receive any kind of therapy, 1 who received chemotherapy alone, 4 who received radiotherapy alone, 8 who received chemotherapy and radiotherapy.

Mitotic count. The area with the highest mitotic count was chosen for counting. Score 1, 0–5 mitoses per 10 high-power fields (HPF) (1 HPF = 0.196 mm^2); score 2, 6–10 mitoses/10 HPF; score 3, >10 mitoses/10 HPF. Number of cases scored 1, 2, and 3 was 33, 11, and 11, respectively.

Cellularity. Cellularity was categorized into three groups: score 1, low (19 cases); score 2, moderate (28 cases); score 3, high (8 cases).

Cellular pleomorphism. Degree of cellular pleomorphism was divided into three groups: absent or minimum (39 cases), moderate (15 cases), marked (1 case).

Necrosis. The extent of the necrotic area was estimated on the microscopic slides and was divided into three groups. We used the slide containing the largest extent of necrosis: Score 1, absent or minimal (<15% of tumor tissue) (36 cases); Score 2, moderate (15–50%) (14 cases); Score 3, marked (>50%) (5 cases).

Vascular differentiation. The degree of vascular differentiation was classified into three types: well-differentiated type (21 cases) (Fig. 1), moderately differentiated type (24 cases), and poorly differentiated type (10 cases) (Fig. 2).

Nonspecific histologic diagnosis. Based on the shape of nucleus and cytoplasm of tumor cells, all cases were divided into four types: spindle-cell tumor (36 cases), pleomorphic tumor (1 case), epithelioid cell tumor (12 cases), and unclassified tumor (6 cases).

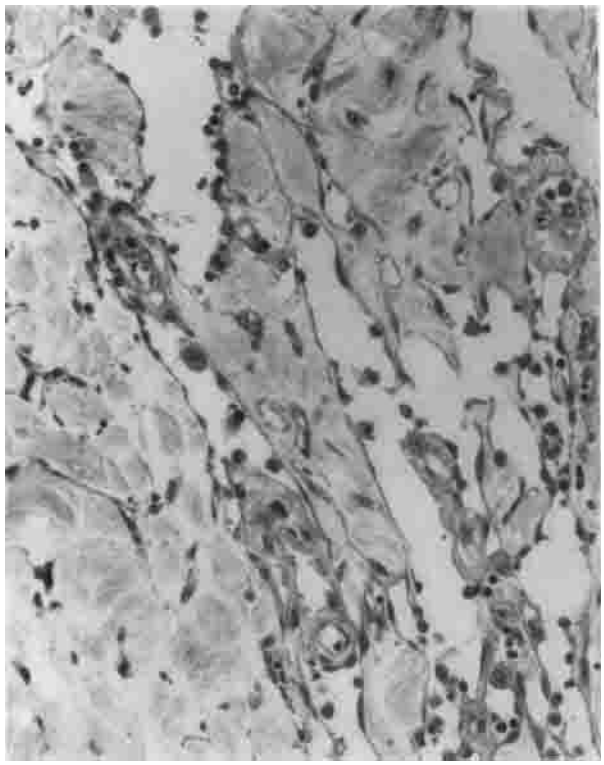

Fig. 1. Well-differentiated angiosarcoma. Irregular but well-developed vascular channels lined by atypical endothelial cells. H & E, × 300.

Statistical Methods

The follow-up period calculated from the date of first admission ranged from 0 to 100 months (median, 11 months) for all patients, and from 1 to 31 (median, 10 months) for eight survivors. Actuarial survival curves were calculated by the method of Kaplan and Meier [19], and the differences were compared by the log-rank test to analyze the significant prognostic factors [20]. Death due to tumor was defined as death directly attributable to the spread of disease, not including death due to complication of treatment such as bleeding, infection, or organ failure caused by the toxicity of chemotherapeutic agents. The actuarial overall survival rates at 2 years in all patients were 21%, and 19% in the patients from the *Annual* and 29% in others: the difference between these figures was not significant ($P = 0.7$).

Multivariate analysis was performed including factors that were significant in the univariate analysis. Multivariate analysis was performed by Cox's proportional hazards model [21], using the SAS program [22] with stepwise manner to identify the independent prognostic factors for overall survival. Prognostic factors, significant at $P < 0.05$ in the stepwise proportional-hazards-model analysis, were selected as being important in influencing survival.

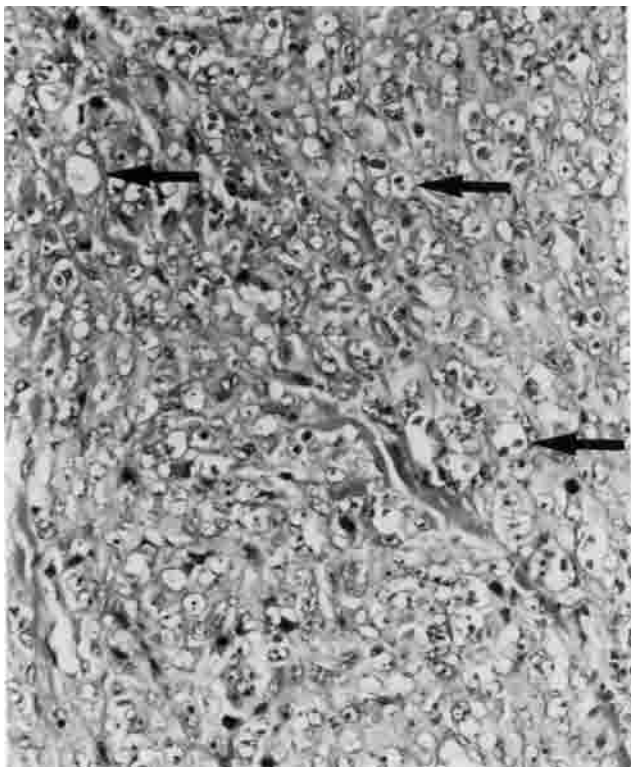

Fig. 2. Poorly differentiated angiosarcoma. Solid sheets of large epithelioid cells with vesicular nuclei and a striking nucleolus. Formation of poorly developed vascular lumina was found (arrows). H & E, × 300.

RESULTS

Univariate Analysis

The prognostic significance of each clinical or histologic factor for overall survival is shown in Tables III and IV.

Clinical factors. Patients with tumors measuring 5 cm or less showed a significantly better prognosis than those with tumors larger than 5 cm ($P < 0.01$). Chi-square test revealed that the tumor size did not correlate with the interval between start of symptoms and admission ($P = 0.4$). Patients aged ≤50 years showed a significantly better prognosis than those aged >50 years ($P < 0.05$). Patients treated with marginal or wide local excision, or amputation followed by chemotherapy or combined chemo- and radiotherapy (multimodal treatment) had a significantly better prognosis than those treated by other methods ($P < 0.05$). Other clinical factors including sex, location, depth, presenting symptoms, interval between start of symptoms and admission, any surgical procedures, adjuvant chemotherapy, and adjuvant radiotherapy alone were not significant for survival. Administration of IL-2 also was not significant for survival ($P = 0.7$).

TABLE III. Actuarial Survival Rates of 55 Patients With Angiosarcoma According to Various Clinical Factors

Clinical factors	No. of patients	Two-year survival rate	*P* value
Sex			
Male	32	14	0.1
Female	23	27	
Age			
≤50 years	10	46	<0.05
>50 years	45	12	
Location			
Head and face	32	13	0.6
Others	23	24	
Size			
≤5 cm	30	27	<0.01
>5 cm	25	9	
Depth			
Superficial	40	21	0.3
Deep	15	13	
Presenting symptoms			
Tumor only	31	22	0.3
Other with or without tumor	24	12	
Interval between start of symptoms and admission			
Less than 1 year	43	18	0.7
More than 1 year	12	20	
Surgical procedure			
Adequate surgery[a]	35	24	0.1
Inadequate surgery[b]	20	7	
Adjuvant chemotherapy			
Performed	35	24	0.2
Not performed	20	8	
Administration of IL-2			
Performed	21	20	0.7
Not performed	34	21	
Adjuvant radiotherapy			
Performed	32	20	0.6
Not performed	23	16	
Mode of treatment			
Multimodal[c]	22	29	<0.05
Others	33	9	

[a] Marginal or wide local excision, or amputation.
[b] Biopsy or intralesional excision.
[c] Marginal or wide local excision, or amputation followed by chemotherapy with or without radiotherapy.

Histologic factors. The patients with low or moderate mitotic counts (≤10/10HPF) showed a better prognosis than those with high counts (>10/10HPF) ($P < 0.01$). Other histologic factors were not significant for survival.

The univariate analysis revealed that age, tumor size, mode of treatment, and mitotic counts were significant for survival. These four factors were included in the multivariate analysis.

Multivariate Analysis

Multivariate analysis was performed on 55 patients with full information and the results are shown in Table V. Tumor size, mode of treatment, and mitotic counts were independent factors significant for survival of pa-

TABLE IV. Actuarial Survival Rates of 55 Patients With Angiosarcoma According to Various Histologic Factors

Histologic factors	No. of patients	Two-year survival rate	*P* value
Cellularity			
Low	19	20	0.6
Moderate or high	36	21	
Mitosis			
≤10/10HPF[a]	44	25	<0.01
>10/10HPF	11	0	
Cellular pleomorphism			
Absent or minimum	39	20	0.5
Moderate or marked	16	13	
Necrosis			
Absent or minimum	36	22	0.5
Moderate or marked	19	12	
Vascular differentiation			
Well-differentiated	21	18	0.7
Moderately or poorly differentiated	34	18	
Nonspecific histologic diagnosis			
Epithelioid pattern	12	9	0.2
Others	43	21	

[a] HPF, high-power fields.

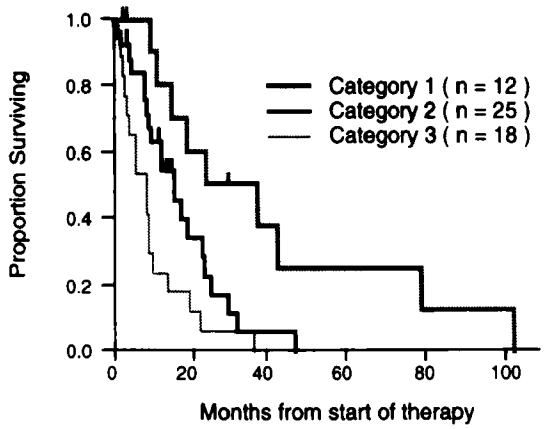

Fig. 3. Two-year survival rate of patients in category 1, 2, and 3 was 50%, 17%, and 5%, respectively.

tients with AS. The coefficient values of these three factors were almost identical. According to the results of the multivariate analysis, a new classification was introduced: one point was given for tumor size >5 cm, nonmultimodal treatment, and mitotic counts >10/10HPF, respectively. The points were added up, and finally 55 patients were divided into three categories; Category 1: point 0, Category 2: point 1, Category 3: point 2 and 3. The 2-year survival rate in patients with category 1, 2, and 3 was 50%, 17%, and 5%, respectively (Fig. 3). The odds ratio of the group was calculated to be 22.3.

DISCUSSION

The cases of AS based mainly on the *Annual of Pathological Autopsy Cases in Japan* seems to reflect the actual incidence because (1) AS is a fatal disease, and (2) autopsy is likely to be carried out on most patients with AS because of its relative rarity. Most of the patients with hepatic or cardiac AS were diagnosed at autopsy; they were therefore excluded from the current study. There was no significant difference in 2-year survival rate between the patients from the *Annual* and others included in the study.

The previous univariate analysis of AS of breast, skin, and soft tissue, or face and scalp suggested the size of the primary tumors to be a prognostic factor [3–5]. The present multivariate analysis confirmed the prognostic significance of tumor size in AS: small-size tumors were more accessible to surgical treatment. No correlation between tumor size and interval between start of symptoms and admission was found, suggesting the importance of early diagnosis and treatment.

Steingaszner et al. [3] suggested the mitotic counts to be a prognostic factor for AS, although failing to confirm the statistical significance because of the small number of cases available in their study. Maddox and Evans [4], however, reported that mitotic counts were not a prognostic factor for AS. As a reason for this discrepancy, Maddox and Evans [4] indicated that mitotic activity varied tremendously within individual cases, enough to influence the counts when only small specimens were available. In addition, Holden et al. [5] pointed out that the histologic features of AS tend to vary greatly from area to area in large specimens. Therefore, they recommend a more extensive histologic examination and a multiblock analysis. The present study of adequate specimens, taken at autopsy or surgery, confirmed the prognostic utility of mitotic counts in AS.

Some investigators reported that the histologic grade of AS determined by the mitotic counts, vascular differentiation, and other factors such as endothelial tufting, papillary formation, necrosis, hemorrhage, and cellular pleomorphism to be indicators for survival [6–8]. The present study did not confirm the prognostic significance of any of these histologic factors other than mitotic counts. These results suggest that mitotic counts is the most significant factor for histologic grading of AS.

Karpeh et al. [10] reported that the curative treatment significantly improved the survival of patients with malignant vascular tumors. The current study did not confirm the favorable effect of surgery alone on AS. The efficacy of adjuvant chemotherapy for patients with AS is controversial; some have reported no beneficial effect [10], but others have reported that administration of actinomycin D reduced the mortality [6,23]. In the current study, two patients given actinomycin D showed relatively longer survivals, i.e., 22 and 46 months. Usefulness of actinomycin D in the treatment of AS should be further evaluated. The present multivariate analysis revealed that the multimodal treatment including wide local excision or

TABLE V. Multivariate Analysis of Prognostic Factors in 55 Patients With Angiosarcoma

Factors	Category	Coefficient	Odds ratio	95% confidence interval
Size	0: ≤5cm 1: >5cm	0.9890	2.689	1.402–5.235
Mitosis	0: ≤10/ 10HPF[a] 1: >10/ 10HPF	0.9634	2.621	1.106–5.740
Mode of treatment	0: multimodal[b] 1: others	0.8142	2.257	1.211–4.294

[a] HPF, high-power fields.
[b] Marginal or wide local excision, or amputation followed by chemotherapy with or without radiotherapy.

amputation followed by chemotherapy with or without radiotherapy to be an independent favorable prognostic factor in AS.

Interleukin-2 (IL-2) is known as one of cytokines that induce activity of lymphokine activated killer (LAK) cells, natural killer cells, cytotoxic T lymphocytes, collectively called IL-2 activated killer cells (IAK cells) [24–26]. Through trials of adoptive immunotherapy, it was evident that LAK therapy induced vascular leakage syndrome, suggesting that IAK cells induced by IL-2 damaged the vascular endothelial cells. Based on this theory, administration of IL-2 on AS was started in Japan [27–29]. In the current study, 21 patients receiving IL-2 did not show a significantly better prognosis than those without IL-2.

In conclusion, multivariate analysis of patients with AS showed that the tumor size, mode of treatment, and mitotic counts are the independent factors significant for prognosis.

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